REMARKS

Entry of the foregoing and further and favorable reconsideration of the subject application in light of the following remarks pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested.

By the foregoing amendment, claims 18, 23, 25, 29, 33, 36-38, and 41-43 have been amended merely to clarify the present invention. Furthermore, new claims 45-55 have been added. Support for new claims 45-52 may be found, at the very least, on page 2, line 6, to page 3, line 23, of the specification as filed. New claim 53 finds support on page 2, line 10, of the specification as filed. New claim 54 finds support on page 2, lines 6-54, of the specification as filed. New claim 55 finds support on page 3, lines 14-16, of the specification as filed. No new matter has been added by the present amendment.

Rejection of Claims 1-53 Under 35 U.S.C. § 112, First Paragraph

Claims 1-53 have been rejected under 35 U.S.C. § 112, first paragraph, for purportedly not being enabled for the full scope of the claims. For at least all of the reasons set forth below, withdrawal of this rejection is believed to be in order.

Applicants respectfully submit that the specification as filed does indeed enable the full scope of the claims. The Examiner states that the invention is limited to liposomes made with specific phospholipids (see the Official Action at page 3). However, the liposomes referred to by the Examiner are merely preferred and are not required. (See, e.g., page 4, lines 48-49, and page 4, line 66, to page 5, line 7).

The Examiner also purports that the adverse physiological reactions to be treated by the present invention are limited to a drop in blood pressure (see the Official Action at page 3). However, adverse physiological reactions are more broadly defined in the specification at page 4, lines 38-47, as follows:

> The term "adverse physiological reaction" includes, but is not limited to clinical symptoms such as lethargy, cyanotic gingival membranes, nausea, vomiting, defecation, diarrhea, rise in body pain, gastrointestinal disturbances, respiratory distress, hematological reactions such as neutropenia, thrombocytopenia, cardiovascular responses such as transient hypotension, vasodilation and transient cardiac changes.

The Examiner further purports that the specification is limited to the administration of the anti-inflammatory agent indomethacin (see the Official Action at page 3). However, the specification clearly defines and describes the anti-inflammatory agents which can be used in conjunction with the present invention much more broadly. See page 12, lines 16-20, of the specification ("In one embodiment of the invention, the anti-inflammatory agent is a steroid; in an alternative embodiment of the invention, the anti-inflammatory agent is a nonsteroidal anti-inflammatory agent. Preferably, the nonsteroidal anti-inflammatory agent is indomethacin,"). Nonsteroidal anti-inflammatory agents are a well known and defined class of compounds. Similarly, steroids are a well known and defined class. Therefore, the specification is enabled for the administration of a broad range of anti-inflammatory agents, and is not just limited to the use of indomethacin (which was only disclosed in the specification as being a preferred anti-inflammatory agent).

Applicants respectfully submit that the specification as filed fully enables the scope of the pending claims. "All that is necessary [for enablement] is that one skilled in the art

be able to practice the claimed invention, given the *level of knowledge and skill* in the art. Further, the scope of enablement must *only bear a "reasonable correlation"* to the scope of the claims." MPEP § 2164.08 (emphasis added). In the present application, such "reasonable correlation" is provided by applicant's disclosed examples and findings. To the extent that experimentation may be required for one to practice other embodiments of applicants' invention, one of ordinary skill in the art would be well-equipped to make and use the entire scope of the claimed invention without the undue level of experimentation indicative of a non-enabling disclosure. *Id.* Applicants submit that it is well within the ability of one of ordinary skill in the art to practice the full scope of the invention as claimed by routine experimentation, given the high level of knowledge and skill in the art. MPEP § 2164.06 ("guidance and ease in carrying out an assay to achieve the claimed objectives" is an issue that may be considered).

While the Examiner has suggested limiting the invention to "liposomes made with specific phospholipids" (see the Official Action at page 3), applicants respectfully submit that such a limitation is improper and unnecessary. Applicants are not required to limit their claims to what they specifically have found will work or to "preferred" embodiments. MPEP § 2164.08, citing *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976).

The Examiner has stated that the claims are not supported by the specification. However, the Examiner has not presented any evidence to support this rejection. Applicants respectfully point out that it is well-established that when the Patent Office rejects a claim on the basis of non-enablement, it is required "to explain why it doubts the

truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. MPEP § 2164.04, citing *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971), emphasis added. The Examiner "should **never** make the determination [of non-enablement] based on personal opinion." MPEP § 2164.05 (emphasis in original). This is because the applicant is entitled to a presumption of an accurate disclosure. MPEP § 2164.04. In the absence of some evidence arising from either a reference or an affidavit from the Examiner under 37 C.F.R. § 1.104(d)(2), the rejection of the claims under 35 U.S.C. § 112, first paragraph, is improper, and applicants respectfully request that it be withdrawn.

Rejection of Claims 45 and 47 Under 35 U.S.C. § 102(b)

Claims 45 and 47 have been rejected under 35 U.S.C. § 102(b) for purportedly being anticipated by JP 60152414 and JP 63264517. For at least all of the reasons set forth below, withdrawal of this rejection is believed to be in order.

Claims 45 and 47 are drawn to a pharmaceutical composition comprising:

(i) a bioactive agent containing liposome; and

(ii) an anti-inflammatory agent.

The anti-inflammatory agent in a pharmaceutical composition of claims 45 and 47 is not encapsulated by the liposome, and therefore is outside of the liposome.

Both of the patents cited by the Examiner (i.e., JP 60152414 and JP 63264517) disclose liposomes containing indomethacin. Neither of the cited patents disclose or

suggest a pharmaceutical composition that comprises an anti-inflammatory agent outside of the liposome. As mentioned above, in the composition of claims 45 and 47 the anti-inflammatory agent is outside of the liposome. Since neither of the cited patents disclose a pharmaceutical composition that comprises an anti-inflammatory agent outside of a bioactive agent containing liposome, neither of these references anticipates the claimed invention.

In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 102(b).

Rejection of Claims 18-19, 21, 23-25, 27, 33-36, 43-45 and 53 Under 35 U.S.C. § 102(b)

Claims 18-19, 21, 23-25, 27, 33-36, 43-45 and 53 have been rejected under 35 U.S.C. § 102(b) for purportedly being anticipated by Young (5,023,087). For at least all of the reasons set forth below, withdrawal of this rejection is believed to be in order.

The present invention is drawn to liposome compositions comprising (i) a liposome encapsulated bioactive agent; and (ii) an anti-inflammatory agent. The present invention is also drawn to methods of treating an animal with a bioactive agent by administering to an animal the liposome composition of the present invention.

Young discloses a method of treatment which involves the use of a composition comprising (i) an aqueous suspension of liposomes containing a drug in entrapped form; and (ii) a large amount of empty liposomes. The drug entrapped by liposome can be an anti-inflammatory drug, such as a steroid.

First, applicants will discuss this rejection as it applies to the composition claims, i.e. claims 25, 27, 33-36, 43-45 and 53.

Young does not disclose a composition comprising (i) a liposome encapsulated bioactive agent and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome. Although the Examiner purports that the liposome encapsulated anti-inflammatory agent disclosed by Young is analogous to the free standing anti-inflammatory agent disclosed by the present invention, and that the empty (water containing) liposomes are analogous to the liposome encapsulating a bioactive agent disclosed by the present invention, this is not a proper comparison. Persons of ordinary skill in the art would in no way consider water as a bioactive agent, as that term is used in the art and within the context of the present specification (see page 7, first full paragraph, where a bioactive agent is defined as a compound or composition of matter having some biological activity in animals; also note the list of possible bioactive agents, said list being completely incompatible with the possibility of water being a bioactive agent). Therefore, Young does not disclose liposome compositions comprising (i) a liposome encapsulated bioactive agent; and (ii) an anti-inflammatory agent.

Next, applicants will discuss the rejection as it applies to the method claims, i.e. claims 18, 19, 21, 23 and 24.

Even if the compositions disclosed by Young were the same as the compositions of the present invention (which clearly they are not), a new method of using such compositions would not necessarily be anticipated by Young unless there was some suggestion in the reference regarding that use. The Examiner purports that any adverse

reaction caused by liposomes is inherent in Young, whether recognized or not. However, there is no evidence of adverse reactions disclosed or inherent in Young. There is no indication that Young recognized such an effect. Furthermore, there is no disclosure in Young that the administration of such anti-inflammatory agents would cause a reduction of adverse physiological effects caused by the liposome composition.

Young disclose administering to an animal (i) a liposome encapsulated drug; and (ii) an empty liposome. The disclosure of Young only refers to the delivery of one compound encapsulated by the liposome, and there is no disclosure that different compounds encapsulated by liposomes could be administered simultaneously. If Young had recognized that the administration of the liposomes resulted in adverse reactions, and that the anti-inflammatory agents would cause a reduction in this reaction, they surely would not have just administered the liposome encapsulated anti-inflammatory agent together with an empty liposome. Such an approach would serve no beneficial effects to the animal, other than to cure a reaction that would not have been present without the treatment. Thus, if one were to administer a (i) liposome encapsulated anti-inflammatory agent; and (ii) an empty liposome, in accordance with the disclosure of Young, it would essentially serve no purpose. Young does not explicitly or inherently disclose the present invention and therefore cannot possibly anticipate the claims.

If Young did not recognize the adverse reactions caused by liposomes or the curative effect the anti-inflammatory agents would have on these adverse reactions, how could Young possibly suggest a method for treating an animal with a bioactive agent comprising administering to said animal (i) a liposome composition; and (ii) an anti-

inflammatory agent? Even if the effects of the liposomes and the anti-inflammatory agents were inherent in Young, there would have to be some recognition by Young of these effects to even suggest the claimed methods. Since there is no recognition, Young could not possibly anticipate the method claims of the present invention.

For at least all of the reasons set forth below, withdrawal of this rejection under 35 U.S.C. § 102(b) is respectfully requested.

Rejection of Claims 18-32, 34-35, 41-42, 45, 47 and 53 Under 35 U.S.C. § 103(a)

Claims 18-32, 34-35, 41-42, 45, 47 and 53 have been rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Young (5,023,087) by itself or in combination with JP 60152414 and JP 63264517. For at least all of the reasons set forth below, withdrawal of this rejection under 35 U.S.C. § 103(a) is believed to be in order.

As stated in more detail above, Young does not disclose or suggest each of the elements of the present invention. Specifically, Young fails to disclose or suggest a composition comprising (i) a liposome encapsulated bioactive agent and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome. Furthermore, Young fails to disclose or suggest methods of treating animals comprising administering a liposome composition comprising (i) a liposome encapsulated bioactive agent and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome. Since there is no suggestion in Young to make the composition of the present invention or to use the composition of the present invention in the methods of the present invention, Young by itself does not render obvious the claimed inventions.

Furthermore, neither of the cited Japanese patents cure the deficiencies of Young. As discussed above, neither of the Japanese patents disclose or suggest a pharmaceutical composition that comprises an anti-inflammatory agent outside of the liposome. Thus, even if the disclosures of either or both of the Japanese patents were taken together with the disclosure of Young, one of skill in the art would not be motivated to make the compositions of the present invention. This is because the compositions of the claim invention require that the anti-inflammatory agent not be encapsulated by a liposome, and both Young and the Japanese patents disclose that the anti-inflammatory agent is encapsulated by a liposome. Therefore, the present invention is not obvious in view of Young alone or in combination with the Japanese patents.

In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

Rejection of Claims 33-44 and 48-52 Under 35 U.S.C. § 103(a)

Claims 33-44 and 48-52 have been rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over Young (5,023,087) in view of Park et al (*Biochim. Biophys. Acta 1108*:257-260 (1992); or alternatively, Park et al in view of Young. For at least all of the reasons set forth below, withdrawal of this rejection of the claims is believed to be in order.

As discussed in more detail above, the present invention is drawn to liposome compositions comprising (i) a liposome encapsulated bioactive agent; and (ii) an anti-inflammatory agent. Claims 33-44 and 48-52 of the present application further recite that

the liposomes in the compositions of the present invention comprise a lipid bilayer having a lipid and a surface agent-modified molecule.

Young does not disclose or suggest each of the elements of the present invention. Specifically, Young fails to disclose or suggest a liposome composition comprising (i) a liposome encapsulated bioactive agent and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome. Since Young fails to disclose the basis of the present invention, Young could not possibly disclose the invention of claims 33-44, which require that the liposome encapsulating the bioactive agent comprises a lipid bilayer having a lipid and a surface agent-modified molecule.

Park et al does not cure the deficiencies of Young. Specifically, Park et al fails to disclose or suggest a liposome composition comprising (i) a liposome encapsulated bioactive agent and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome. If the disclosures of Park et al and Young were taken together, one would arrive at a composition comprising (i) an empty liposome modified with carboxylic acids; and (ii) a liposome encapsulated anti-inflammatory agent, wherein the liposome is modified with carboxylic acids. This is not even close to the compositions claimed by the present invention. Furthermore, there is nothing in either Park et al or Young which suggest the compositions of the claimed invention.

Therefore, even if the disclosures of Park et al and Young were taken together, one would not arrive at the compositions of the present invention. This is because neither Park et al or Young disclose or suggest a liposome composition comprising (i) a liposome

encapsulated bioactive agent and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome.

In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

Rejection of Claims 29-32 and 46 Under 35 U.S.C. § 103(a)

Claims 29-32 and 46 have been rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over JP 63264517 or Young; each alone or in combination with Park et al or in combination with Park et al and further in combination with Cheng et al (*Investigative Radiology* 22:47-55 (1987)). For at least all of the reasons set forth below, withdrawal of this rejection under 35 U.S.C. § 103(a) is believed to be in order.

The invention claimed in claims 29-32 and 46 is drawn to liposome compositions comprising (i) a liposome encapsulated bioactive agent, wherein the bioactive agent is a contrast agent; and (ii) an anti-inflammatory agent.

As discussed in more detail above, neither Young or JP 63264517 disclose or suggest liposome compositions comprising (i) a liposome encapsulated bioactive agent; and (ii) an anti-inflammatory agent. Furthermore, neither of these references disclose or suggest such a composition wherein the bioactive agent is a contrast agent. Therefore, neither of these references taken alone would disclose or suggest the claimed invention.

Park et al does not solve the deficiencies of these two references. Park et al merely discloses that carboxylic acids can prolong the circulation of liposomes. Park et al does not disclose or suggest a liposome composition comprising (i) a liposome encapsulated

bioactive agent, wherein the bioactive agent is a contrast agent; and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome. Therefore, since neither Young, JP 63264517 or Park et al disclose or suggest a liposome composition comprising (i) a liposome encapsulated bioactive agent, wherein the bioactive agent is a contrast agent; and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome, none of these references, either taken alone or together, would render the present invention obvious.

Finally, Cheng et al does not cure the deficiencies of JP 63264517, Young or Park et al. Cheng et al merely discloses that contrast agents may be encapsulated by liposomes. Cheng et al does not disclose or suggest a liposome composition comprising (i) a liposome encapsulated bioactive agent, wherein the bioactive agent is a contrast agent; and (ii) an anti-inflammatory agent, which is not encapsulated by a liposome. Therefore, Cheng et al does not solve the deficiencies of the other references, and even if the disclosures of each of these references were taken together, one would not arrive at the compositions of the present invention.

In light of these remarks, applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 103(a).

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Amendment and Reply dated August 27, 2001

Marked-up Claims 18, 23, 25, 29, 33, 36-38, and 41-43

18. (Amended) A method of treating an animal with a bioactive agent comprising administering to said animal [an anti-inflammatory agent and] a liposome composition, wherein said liposome composition induces an adverse physiological reaction in said animal[;] in the absence of an anti-inflammatory agent, and wherein said liposome composition comprises a liposome entrapped bioactive agent; and administering to said animal an anti-inflammatory agent wherein [reducing] said adverse physiological reaction is reduced.

23. (Amended) A method of treating an animal with a bioactive agent comprising administering to said animal a composition comprising:

(i) a liposome; and

(ii) an anti-inflammatory agent[,];

wherein said liposome composition induces an adverse physiological reaction in said animal[;] in the absence of an anti-inflammatory agent; thereby [and] reducing said adverse physiological reaction.

25. (Amended) A composition comprising a liposome [and a bioactive agent which is] in combination with an anti-inflammatory agent not contained in the liposome.

Attachment to Amendment and Reply dated August 27, 2001

Marked-up Claims 18, 23, 25, 29, 33, 36-38, and 41-43

29. (Amended) A [liposome] composition comprising (i) a liposome composition, and (ii) [and a bioactive agent which is a contrast agent, in combination with] an anti-inflammatory agent, wherein said liposome composition comprises a liposome encapsulated contrast agent.

33. (Amended) The composition of claim [25] 29 wherein the liposome comprises a lipid bilayer having a lipid and a surface agent-modified molecule which comprises an anchor and a surface modifying agent, [agent modified molecule, wherein the anti-inflammatory agent is administered to the animal prior to administration of the liposome composition and] wherein the liposome has an average diameter of from at least about 220 nm to about 5000 nm.

36. (Amended) The composition of claim [25] 33, wherein the concentration of surface agent modified molecule in the bilayer is at least about 2 mole percent.

37. (Amended) The composition of claim [25] 33, wherein the surface modifying agent is a dicarboxylic acid, a monocarboxylic acid or a sulfolipid.

38. (Amended) The composition of claim [25] 33, wherein the surface modifying agent is a dicarboxylic acid.

Attachment to Amendment and Reply dated August 27, 2001

Marked-up Claims 18, 23, 25, 29, 33, 36-38, and 41-43

41. (Amended) The composition of claim [25] 33, wherein the anchor is a phosphatidylethanolamine.

42. (Amended) The composition of claim 41, wherein the phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine.

43. (Amended) The composition of claim 25, wherein said liposome comprises a lipid bilayer having a lipid and a surface modified molecule, said [the] surface agent modified molecule comprising [comprises] a phospholipid anchor having a glycerol backbone [backbone] and a spacer group, and wherein said [the] spacer group comprises a functional group capable of attaching to the glycerol backbone and a functional group capable of attaching to the phosphate group of the phospholipid anchor.